

CLAIMS:

1. Isolated endostatin.
- 5 2. The isolated endostatin of Claim 1 comprising, an isolated protein that is approximately 18 kDa as determined by non-reduced gel electrophoresis, and approximately 20 kDa as determined by reduced gel electrophoresis, wherein the protein 10 can be isolated from the murine hemangioendothelioma EOMA cell line, and wherein the protein is further characterized by its ability to specifically inhibit proliferating cultured endothelial cells.
- 15 3. The endostatin of Claim 1, wherein the N-terminal amino acid sequence of the protein has substantial sequence homology to Seq ID No:1.
- 20 4. The endostatin of Claim 1, wherein the protein has substantial sequence homology to a C-terminal peptide fragment of collagen type XVIII.
- 25 5. The endostatin of Claim 1 made by a process comprising recombinantly producing the protein of Claim 1 in a recombinant expression system, and isolating the recombinantly produced protein in its un-refolded form.
- 30 6. The endostatin of Claim 5, wherein the recombinant expression system is *E. coli* or baculovirus.
7. A compound comprising, an isolated nucleic acid sequence coding for endostatin protein.

8. The compound of Claim 7, wherein the endostatin protein is approximately 18 kDa as determined by non-reduced gel electrophoresis, and approximately 20 kDa as determined by reduced gel electrophoresis, wherein the protein can be isolated from the murine hemangioendothelioma EOMA, and wherein the protein is further characterized by its ability to specifically inhibit proliferating cultured endothelial cells.

9. The compound of Claim 7, wherein the N-terminal amino acid sequence of the protein has substantial sequence homology to Seq ID No:1.

10. The compound of Claim 7, wherein the protein has substantial sequence homology to a C-terminal peptide fragment of collagen type XVIII.

11. A compound comprising,
an isolated antibody capable of specifically binding to endostatin protein.

12. The compound of Claim 11, wherein the endostatin protein is approximately 18 kDa as determined by non-reduced gel electrophoresis, and approximately 20 kDa as determined by reduced gel electrophoresis, wherein the protein can be isolated from the murine hemangioendothelioma EOMA, and wherein the protein is further characterized by its ability to specifically inhibit proliferating cultured endothelial cells.

13. The compound of Claim 11, wherein the antibody is a monoclonal antibody.

14. The compound of Claim 11, wherein the N-terminal amino acid sequence of the endostatin protein has substantial sequence homology to Seq ID No:1.

15. The compound of Claim 11, wherein the endostatin protein has substantial sequence homology to a C-terminal peptide fragment of collagen type XVIII.

5 16. An isolated endostatin made by a process comprising,

a. collecting culture media used to grow murine hemangioendothelioma cell line EOMA; and

b. fractionating the media by heparin column

10 chromatography,

wherein the isolated endostatin is a protein that is approximately 18 kDa as determined by non-reduced gel electrophoresis, and approximately 20 kDa as determined by reduced gel electrophoresis, and the protein is capable of specifically inhibiting 15 endothelial cell proliferation in cultured cells.

17. A method of treating an angiogenesis-related disease comprising,

20 administering to a patient in need of such treatment of the endostatin of ~~Claim 1~~ in an amount sufficient to inhibit angiogenesis.

25 18. The method of Claim 17, wherein the endostatin is a recombinantly produced protein, and wherein the recombinantly produced protein is administered in its un-refolded form.

30 19. The method of Claim 18, wherein the recombinantly produced endostatin provides a sustained release of the protein over a period of at least 8 hours.

35 20. The method of Claim 17, wherein the angiogenesis-related disease is selected from the group consisting of angiogenesis-dependent cancers; benign tumors; rheumatoid arthritis; psoriasis; ocular angiogenesis diseases; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac

joints; angiofibroma; wound granulation; intestinal adhesions, atherosclerosis, scleroderma, hypertrophic scars, cat scratch disease and *Helobacter pylori* ulcers.

5 21. The method of Claim 20, wherein the angiogenesis-related disease is angiogenesis-dependent cancer.

10 22. A method of treating a patient with an angiogenesis-dependent cancer tumor comprising,

15 administering to a patient in need of such treatment of the endostatin of Claim 1 in an amount sufficient to cause tumor regression.

20 23. The method of Claim 22, wherein the endostatin is a recombinantly produced protein, and wherein the recombinantly produced protein is administered in its un-refolded form.

25 24. The method of Claim 23, wherein the recombinantly produced protein provides a sustained release of the protein for a period of at least 8 hours.

30 25. A method of curing a patient with an angiogenesis-dependent cancer comprising,

35 administering to a patient in need of such a cure an angiogenesis-dependent cancer curing amount of a composition comprising,

40 angiostatin combined with the endostatin of Claim 1, wherein the angiostatin and the endostatin are provided in amounts such that the composition is capable of effectively inhibiting angiogenesis of angiogenesis-dependent cancers when administered to patients with angiogenesis-dependent cancers.

45 26. The method of Claim 25, wherein at least one of angiostatin and endostatin is a recombinantly produced protein, and

wherein the recombinantly produced protein is administered in its un-refolded form.

27. The method of Claim 25, wherein the recombinantly
5 produced protein provides a sustained release of the protein for a period
of at least 8 hours.

28. A method of birth control comprising,
administering to a female an amount of the
10 endostatin of Claim 1 sufficient to prevent embryo implantation.

29. The method of Claim 28, wherein the endostatin is
recombinantly produced protein, and wherein the recombinantly
produced protein is administered in its un-refolded form.

15 30. The method of Claim 29, wherein the recombinantly
produced protein provides a sustained release of the protein for a period
of at least 8 hours.

20 31. A composition comprising,
angiostatin combined with the endostatin of Claim 1,
wherein the angiostatin and the endostatin are provided in amounts such
that the composition is capable of effectively regressing the tumor mass
25 of angiogenesis-dependent tumors when administered to patients with an
angiogenesis-dependent tumor.

30 32. A method of making endostatin protein comprising,
recombinantly expressing a protein that is
approximately 18 kDa as determined by non-reduced gel
electrophoresis, and approximately 20 kDa as determined by reduced gel
electrophoresis, and which has substantial sequence homology to
endostatin, the protein being further characterized by its ability to
specifically inhibit proliferating cultured endothelial cells.

33. The method of Claim 32, wherein the endostatin protein is produced in an ~~expression system selected from the group consisting of bacterial expression systems, yeast expression systems and insect viral expression systems.~~

5

